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Attorney's Docket No. 5470.148CX PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Baldwin, et al.		
Serial No.:	08/959,160	Group No.:	1636
Filed:	October 28, 1997	Examiner:	T. McKelvey
For:	**USE OF NF-$_6$B INHIBITION IN COMBINATION THERAPY FOR CANCER**		

October 18, 2000

Commissioner for Patents
Washington, DC 20231

Response to Official Action

Dear Sirs:

This is in response to the Official Action of March 16, 2000

Remarks

Claims 1-12 and 14-28 stand rejected as unenabled. In the official action, it is stated (among other things) that the nature of the invention is complex because it is a method to be used to treat cancer, it is stated that the specification does not provide a working example, and it is suggested that the specification only provides prophetic guidance concerning how to use the claimed method to treat cancer. For the reasons set forth below, reconsideration of this rejection is respectfully requested.

As an initial matter, applicants will be pleased to submit the information set forth in **Exhibit A**, **Exhibit B** and **Exhibit C**, all of which are discussed below, in a Rule 132 Declaration, if the Examiner so desires.

Applicants would also be pleased to conduct an interview in this case to further discuss the scientific and technical issues raised by the rejection of record, if the Examiner so desires.

In overview, the present invention provides a way to facilitate the cytotoxic effects of chemotherapeutic compounds by inhibiting the transcription factor NF-κB. Resistance of tumors and hematological neoplasms to chemotherapy is a common clinical problem in human cancer. Resistance to chemotherapies may already exist before the initiation of

therapy because of the overexpression of the multidrug resistance gene product MDR1, which functions to export a variety of chemotherapies from tumor cells. Moreover, chemoresistance (acquired or inducible) may develop in response to chemotherapy by other unknown mechanisms. Apoptosis (programmed cell death) is believed to be the main mechanism whereby chemotherapy and radiation induce the killing of tumor cells. Apoptosis also serves as a cell-killing mechanism induced by cytokines such as tumor necrosis factor α (TNFα). Apoptosis induced by TNFα and by chemotherapy and radiation seem to require, at least partially, the activation of the caspase cascade, leading to proteolytic cleavage of a variety of important proteins and ultimately to cleavage of cellular DNA. TNFα, chemotherapy, radiation and other stimuli activate the transcription factor NF-κB, and this response potently suppresses the apoptotic potential of these stimuli *in vitro*.

In light of this chemoresistance response due to the activation of NF-κB, there exists a need for a means to inhibit NF-κB to enhance the effectiveness of chemotherapeutic agents.

The present invention, as defined in the above-referenced patent application, involves inhibiting NF-κB to facilitate the effectiveness of chemotherapeutic agents. The main reason that cancer has been a hard to treat group of diseases is because cancers activate NF-κB in response to the exposure to chemotherapy and radiation. The instant inventors find that cancer cells from a variety of different origins (colorectal, breast, leukemia, brain, etc.) show essentially the same response: Activation of NF-κB in response to standard cancer therapy. In fact, it is now believed that the highly unpredictable nature of cancer therapy is linked to how well cancer therapies activate NF-κB.

In a series of experiments described in Wang *et al.*, *Nature Medicine*. **5**:412-417 (1999), it has been shown that CPT-11, a broad anti-tumor drug, induces NF-κB nuclear translocation in a dose-dependent manner. It has also been demonstrated that the inhibition of NF-κB enhances anti-tumor responses of CPT-11 in HT1080 tumors after subcutaneous injection of cells in nude mice with an adenovirus encoding the 'super-repressor' form of IκBα. Furthermore, tumor growth was enhanced by treatment with CPT-11 alone, but combined systemic CPT-11 treatment and tumor injection with IκBα elicited significant inhibition of tumor growth. It was determined that the anti-tumor affect of NF-κB was elicited by apoptosis rather than necrotic mechanisms.

Moreover, a second tumor model, Lovo colorectal, has also been used to demonstrate that this enhanced anti-tumor response could be attained in other tumor cells. The combination of CPT-11 and IκBα led to a considerable suppression of tumor growth associated with substantially enhanced apoptotic response, whereas CPT-11 or IκBα alone were substantiallyt ineffective at inducing these responses.

Thus, the experiments presented in **Exhibit A** demonstrate that the inhibition of NF-κB activation in tumors, through adenoviral delivery of a modified from of IκBα, functions to substantially enhance the apoptotic potential of cancer therapies.

As described by Cusack *et al. Cancer Res.* 60: 2323-2330 (2000) (copy attached herewith as **Exhibit B**), the viral delivery of an inhibitor to block NF-κB directly in *in vivo* tumors (for gene therapy) or systemically has been demonstrated. Using the LOVO colorectal tumor model, administration of super repressor IκBα in conjunction with CPT-11 substantially reduced tumor size. No undue experimentation beyond what was described in the instant specification was involved. Mice treated every 5 to 10 days in combination with CPT-11 administration over a 50 day period resulted in a persistent tumoricidal response and ultimately sustained remission following cessation of treatment at day 50. Results of this experiment are shown in **Figure 2** in **Exhibit B**. Furthermore, it was demonstrated that adenoviral delivery of the super-repressor IκBα inhibits nuclear translocation of NF-κB induced by CPT-11 *in vivo.* Results of this experiment are shown in **Figure 3** in the attached hereto **Exhibit B**.

Further, combined treatment of CPT-11 and systemically-administered NF-κB inhibitor, PS-341 (a drug developed by Proscript), into LOVO colorectal tumors in mice at various concentrations, demonstrates a direct correlation between the concentration of NF-κB inhibitor and tumor size reduction (copy attached herewith as **Exhibit C**). Still further, this demonstrates that the invention is not limited to adenoviral delivery of the NF-κB inhibitors; the tumor suppression effect is as evident with PS-341 as it is with super-repressor IκBα.

The examiner cites **Bentires-Alj** *et al.* (*Cancer Res.* **59**:811-815, 1999) in the Official Action in the passage beginning at page 7. The experiments described in this paper make use of four different cell lines that were stably-expressing the modified from of IκBα. They determined that stable expression of IκBα did not show enhanced cytotoxicity in response to

chemotherapy even though the chemotherapies activated NF-κB. However, stable inhibition of NF-κB via IκB expression is not a consistent or "real life" experimental approach to test the role of NF-κB in chemoresistance. The Bentires-Alj *et al.* data shows that selected clones that were stably-transfected with mutated IκBα were not more sensitive to the various chemotherapy agents and TNFα, despite activation of NF-κB by these stimuli. This suggests that the process of selecting clones, that contain stable expression of mutated IκBα, lead to the acquisition of alternative survival mechanisms necessary to overcome the NF-κB inhibition that occurs in the presence of constitutively-expressed, mutated IκBα. Bentires-Alj et al. is specifically rebutted by the experimental data set forth in the paper attached in **Exhibit B.**

It is well settled that the enablement requirement can be satisfied in a variety of ways. In the field of biology, it is important that applicants be accorded this flexibility. The Federal Circuit made clear in *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), that biotechnology inventors who publish articles describing technology at an early stage should not plan to rely on arguing those publications are non-enabling when they file a patent application more than one year later. The patent system is not intended to exclude those who work in fields of technology were research findings are regularly published, so long as applicants follow the guidance set forth in the statutes and case authority. In attempting to comply with *In re O'Farrell,* the applicants should not be prejudiced by being limited in the particular manner by which they satisfy the enablement requirement. In this case, it is respectfully submitted that the evidence discussed above confirms that the specification as filed in this case satisfies the enablement requirement set forth in section 112 of the patent statute, and respectfully submitted that this rejection should be withdrawn.

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully Submitted,

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Enclosures: EXHIBITS A-C

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Attention: Office for Petitions, Commissioner for Patents, Box DAC, Washington, DC 20231, on October 18, 2000.

Vickie Diane Prior
Date of Signature: October 18, 2000